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GM-CSF as a Systemic Adjuvant in a Phase II Prostate Cancer Vaccine Trial

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BACKGROUND. Recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF; Leukine® [sargramostim], Immunex Corp., Seattle, WA) was administered to a subgroup of 44 patients in a phase II clinical trial for prostate cancer using DC pulsed with HLA-A2-specific prostate-specific membrane antigen (PSMA) peptides. Our purpose was to determine if GM-CSF caused any enhancement of patients' immune responses, including enhancement of clinical response to the DC-peptide treatment. This report compares the clinical responses to DC-peptide infusions with and without systemic GM-CSF treatment.

METHODS. GM-CSF was administered by subcutaneous injection at a dose of 75 $\mu g/m^2$/day for 7 days with each of six infusion cycles. Prefilled syringes were supplied to the patients for self-administration.

RESULTS. One complete and 8 partial responders were identified among 44 patients who received GM-CSF, as compared to 2 complete and 17 partial responders among 51 patients who did not receive GM-CSF. For patients who received GM-CSF and were tested by delayed-type hypersensitivity (DTH) skin test, 3 cases of improved immune response were identified, compared to 5 cases of improvement in patients who did not receive GM-CSF. The main GM-CSF side effects reported were local reactions at the site of injection, fatigue, pain, and fever. Most reported side effects were of mild severity, with some cases of moderate severity leading to discontinuation of GM-CSF.

CONCLUSIONS. Our results suggest GM-CSF as employed in this trial did not detectably enhance clinical response to DC-peptide infusions, or significantly enhance the measured immune response. *Prostate 39:291–297, 1999.* © 1999 Wiley-Liss, Inc.

KEY WORDS: **granulocyte-macrophage colony-stimulating factor; dendritic cells; prostate-specific membrane antigen; immunotherapy; cancer vaccine; prostate cancer; clinical trial**

INTRODUCTION

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a potent enhancer of hematopoietic differentiation from several lineage precursors, including phagocytic macrophages and dendritic cells (DC) [1]. GM-CSF is a substance which influences the survival, proliferation, differentiation, and functional activation of myeloid hematopoietic cells, and is approved in the United States for use in hematopoietic reconstitution following autologous bone marrow transplantation [2].

When administered in vivo, GM-CSF promotes the growth and antigen-presenting capabilities of DC [3]. Peptide-pulsed DC propagated in GM-CSF have been shown to induce antigen-specific $CD8^+$ T-cells in both

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mice [4] and humans [5]. Administration of systemic GM-CSF (75 μg/m² s.c. over 6 consecutive days) before and after melanoma-associated peptide vaccination enhanced immune responses, including a greater degree of tumor regression, elevated skin test reactions, more antigen-specific CD8⁺ T cells, and increased CD1a⁺ infiltration into skin biopsies [6]. Based on such information, we included GM-CSF as a systemic adjuvant in our phase II prostate cancer clinical trial. This report will compare the responses to DC-peptide infusion for those patients who received GM-CSF and those who did not.

MATERIALS AND METHODS

GM-CSF

Recombinant human GM-CSF (Leukine® [sargramostim]) was provided by Immunex Corp. (Seattle, WA). GM-CSF was administered by subcutaneous injection at a dose of 75 μg/m²/day for 7 days starting on the day of DC-peptide infusion. This dose was selected based on previous peptide vaccine trials using comparable doses of GM-CSF [6]. The first dose of each course was given 1–2 hr prior to DC-peptide infusion and doses were continued daily to complete one 7-day course with each infusion. Following training by a nurse on how to give self-injections, prefilled syringes were supplied to the patients for self-administration. GM-CSF was initially offered to alternative patients until an estimated pool of participants was achieved that would compare with those who did not receive this agent. The selection was not randomized.

DC Culture and Administration of DC Pulsed With PSMA Peptides

DC were cultured, pulsed with PSMA peptides, and administered to patients as previously described [7]. In brief, peripheral blood mononuclear cells (PBMC) were isolated from leukapheresed material, or heparinized whole blood, using Histopaque 1077 Ficoll (Sigma Chemical Co., St. Louis, MO) density gradient. Leukapheresis was performed at the Fred Hutchinson Cancer Research Center (Seattle, WA). Isolated PBMC were then cultured in complete medium (OPTIMEM medium from Gibco-BRL, Grand Island, NY, and 5% heat-inactivated autologous plasma) in a 75-cm² tissue culture flask (2–3 × 10^7 cells/flask), in a humidified incubator (37°C, 5% CO_2) for 60 min. Nonadherent cells were removed, and adherent cells were gently washed with warm (37°C) complete medium. These adherent cells were then cultured for 7 days in DC propagation medium (DCPM: complete medium, 500 units/ml GM-CSF and 500 units/ml IL-4), 10 ml DCPM per flask. After 7 days, cultured DC were pulsed with PSMA peptides (PSM-P1 and PSM-P2) by incubating the cells for 2 hr with 10 μg/ml PSM-P1 and PSM-P2, washing the cells, and resuspending in 10 ml injection-grade saline. The peptide-pulsed DC suspension was delivered to the Northwest Hospital Day Surgery/Short Stay Unit, and infused over 30 min with 100 ml 0.9% saline. Each patient received six infusions of peptide-pulsed DC at 6-week intervals.

Clinical Monitoring

Patients were monitored throughout the course of their six infusions with periodic prostate-specific antigen (PSA; Tandem-E PSA kit, Hybritech Incorporated, San Diego, CA), free-PSA (Tandem-R PSA kit, Hybritech Incorporated), PSMA (in-house Western blot assay), complete blood counts, CHEM-22, bone alkaline phosphatase (Tandem-R Ostase kit, Hybritech Incorporated), chest X-rays, bone scans, and ProstaScint® (Cytogen Corporation, Princeton, NJ) scans [8,9]. Patients were evaluated for clinical and biochemical adverse events. All testing was conducted on an outpatient basis at Northwest Hospital.

Immunological Response Monitoring

A delayed-type hypersensitivity (DTH) test to measure general immune response activity was conducted at the beginning of this trial and repeated after the conclusion of the study. Recall antigens tested were: tetanus, diphtheria, streptococcus, tuberculin, control, candida, trichophyton, and proteus. Reactions to antigens were read 48 hr after injection. Size of indurations were measured and a photograph was taken.

RESULTS

Study Population

This phase II clinical trial was an open-label trial comprised of three main groups of patients. The first group (designated group A-I) consisted of 33 patients with hormone-refractory metastatic prostate cancer who had also participated in our previous phase I study. Another group of 33 patients with hormone-refractory metastatic prostate cancer (designated group A-II) had received no previous immunotherapy. The third group (designated group B) contained 41 patients with locally recurring prostate cancer and no previous immunotherapy. The total number of patients enrolled in the study was 107. To be considered evaluable, patients must have received at least one infusion cycle. By this requirement, group

TABLE I. Comparison of Responses in Patients With and Without GM-CSF Treatment*

Group	Response	Total	%	GM-CSF yes	%	GM-CSF no	%
A-I	CR	0	0	0	0	0	0
	PR	9	27	2	12	7	44
	NC	11	33	6	35	5	31
	P	13	39	9	53	4	25
	Total	33		17		16	
A-II	CR	2	8	1	8	1	8
	PR	6	24	2	15	4	33
	NC	1	4	1	8	0	0
	P	16	64	9	69	7	58
	Total	25		13		12	
B	CR	1	3	0	0	1	4
	PR	10	27	4	29	6	26
	NC	8	22	3	21	5	22
	P	18	49	7	50	11	48
	Total	37		14		23	

*CR, complete response; PR, partial response; NC, no change; P, progression.

A-I had 33 evaluable patients, group A-II had 25 evaluable patients, and group B had 37 evaluable patients. This is the number of evaluable patients (total 95) considered in this report. As previously reported, of evaluable patients in group A-I there were 9 partial responders [7]. In group A-II there were 6 partial responders and 2 complete responders [10]. In group B there were 10 partial responders and one complete responder [11] (Table I).

For each study group, approximately half of the patients received GM-CSF as an adjuvant to six infusions of DC pulsed with two HLA-A2-specific PSMA peptides. In group A-I, 17 patients received GM-CSF, while 16 did not; in group A-II, 13 patients received GM-CSF, while 12 did not; and in group B, 14 patients received GM-CSF, while 23 did not.

Comparisons between each group (A-I, A-II, and B), and among patients with and without GM-CSF treatment, are shown in Table II. Serum prostate markers (PSA and PSMA), hematocrit, lymphocyte count, and patient age were compared. Mean values and standard errors are shown for tests conducted at the beginning of the clinical trial before the first DC-peptide infusion, and age reflects the patients' ages at that same time-point. In group A-I, for patients who received GM-CSF, the mean PSA was 448.151 ng/ml, compared to 157.334 ng/ml for patients who did not receive GM-CSF. In group A-II, mean PSA for patients with GM-CSF was 110.447 ng/ml, and 236.807 ng/ml for patients without GM-CSF. In group B, mean PSA for patients who received GM-CSF was 19.957 ng/ml, and 5.508 ng/ml for those who did not receive GM-CSF. All of the mean PSA values were above the normal range of 0.0–4.0 ng/ml. The mean PSMA (measured as relative intensity level, RIL) for group A-I with GM-CSF was 0.3047, and 0.2772 for patients without GM-CSF; 0.2974 for group A-II with GM-CSF, and 0.3372 for group A-II without GM-CSF; and 0.2277 for group B with GM-CSF, and 0.2696 for group B without GM-CSF. These mean PSMA values were all above the PSMA normal range of 0.1384–0.2198. The mean hematocrit values for groups A-I and A-II were below the normal range of 40–52%. For group A-I with GM-CSF the mean hematocrit was 38.2%, and 38.2% for group A-I without GM-CSF; and 36.5% for group A-II with GM-CSF, and 38.8% for group A-II without GM-CSF. The mean hematocrit values for group B patients were within normal range: 41.2% for patients who received GM-CSF, and 41.8% for those who did not receive GM-CSF. Mean lymphocyte counts for all groups were within the normal range of 1,000–3,500/μl, except for group A-II patients who received GM-CSF. In this group the mean lymphocyte count was 994/μl. The mean age for group A-I with GM-CSF was 72 years, and for group A-I without GM-CSF it was 72 years; group A-II with GM-CSF was 66, and group A-II without GM-CSF was 58; and group B with GM-CSF was 66, and group B without GM-CSF was 66.

Clinical Response

For each group of the phase II study, patients were considered evaluable if they completed at least one infusion cycle. As previously reported [7,10,11], 95 patients were evaluated for response, based on National Prostate Cancer Project (NPCP) criteria, PSA values

TABLE II. Comparison of PSA, PSMA, Hematocrit, Lymphocyte Count, and Age in Each Patient Group, With and Without GM-CSF*

	GM-CSF yes		GM-CSF no	
Group	Mean	SE	Mean	SE
A-I				
PSA	448.151	370.618	157.334	91.457
PSMA	0.3047	0.0309	0.2772	0.0396
Hematocrit	38.2	1.4	38.2	0.9
Lymphocyte	1,135	165	1,202	166
Age	72	2	72	2
No. of patients	17		16	
A-II				
PSA	110.447	69.391	236.807	178.600
PSMA	0.2974	0.0365	0.3372	0.0208
Hematocrit	36.5	1.3	38.8	0.8
Lymphocyte	994	124	1,103	190
Age	66	3	58	3
No. of patients	13		12	
B				
PSA	19.957	12.982	5.508	1.722
PSMA	0.2277	0.0394	0.2696	0.0204
Hematocrit	41.2	0.9	41.8	0.6
Lymphocyte	1,398	150	1,425	133
Age	66	2	66	2
No. of patients	14		23	

*Normal ranges: PSA, 0.0–4.0 ng/ml; PSMA, 0.1384–0.2198 relative intensity level; hematocrit, 40–52%; lymphocyte, 1,000–3,500/μl.

(50% decrease), or significant improvements in repeat ProstaScint® scans. Table I summarizes the responses of patients, divided into the three study groups (A-I, A-II, B), who received GM-CSF compared to those who did not. Patients were evaluated as receiving GM-CSF if they received at least one GM-CSF injection.

In group A-I, 33 patients were evaluated, with 9 patients showing a partial response (27%). For 17 patients who received GM-CSF, 2 (12%) were partial responders, while 7 of 16 (44%) non-GM-CSF patients were partial responders. Group A-II had 25 evaluable patients, 2 of whom were complete responders (8%), and 6 of whom were partial responders (24%), for a total of 8 responders (32%). Of the 13 group A-II GM-CSF patients, one was a complete responder (8%), and 2 (15%) were partial responders. Therefore, 3 of 13 (23%) GM-CSF patients were responders. Of the 12 group A-II non-GM-CSF patients, one (8%) was a complete responder and 4 (33%) were partial responders, for a total of 5 (41%) responders. In group B, 10 out of 37 evaluable patients were partial responders (27%), and one was a complete responder (3%). Of 14 group B patients with GM-CSF, 4 were partial responders (29%). Six of 23 (26%) group B non-GM-CSF patients were partial responders and one (4%) was a complete responder, for a total of 7 (30%) responders.

Immunological Results

For patients in groups A-II and B, immunological responses were tested using a DTH skin test. Patients received skin testing prior to the first infusion and after the sixth infusion. Each test consisted of seven antigens and one control. The number of positive reactions was recorded for each test. To analyze a change in immune response over the course of the phase II trial, the number of positive tests before infusion 1 and after infusion 6 was compared (Table III). Patients were designated as not evaluable if they did not complete six infusions. Group A-I patients did not receive post-infusion-six skin tests, therefore their immune response change was not evaluable.

In group A-II, of 25 patients, one (4%) showed an increase in skin test response, 5 (20%) decreased, 8 (32%) showed no change (the same number of positive reactions before and after six infusions), and 11 (44%) were not evaluable for skin test comparison. Of the 13 group A-II patients who received GM-CSF, none (0%) had an increase in positive skin test reactions, 2 (15%)

TABLE III. Comparison of Skin Test Changes (Prestudy to Poststudy) in Patients With and Without GM-CSF Treatment*

Group	Change	Total	%	GM-CSF yes	%	GM-CSF no	%
A-II	Increase	1	4	0	0	1	8
	Decrease	5	20	2	15	3	25
	NC	8	32	4	31	4	33
	NE	11	44	7	54	4	33
	Total	25		13		12	
B	Increase	7	19	3	21	4	17
	Decrease	13	35	6	43	7	30
	NC	16	43	4	29	12	52
	NE	1	3	1	7	0	0
	Total	37		14		23	

*NC, no change; NE, not evaluable, patient off study before completing six infusions.

decreased, 4 (3%) had no change, and 7 (54%) were not evaluable. One (8%) of the 12 non-GM-CSF group A-II patients showed an increase in skin test response, 3 (25%) showed a decrease, 4 (33%) had no change, and 4 (33%) were not evaluable.

In group B, 7 (19%) of 37 patients had an increased number of positive skin test results, 13 (35%) decreased, 16 (43%) had no change, and one (3%) was not evaluable. Three (21%) of 14 patients who received GM-CSF had an increased immune response, 6 (43%) decreased, 4 (29%) showed no change, and one (7%) was not evaluable. For the 23 non-GM-CSF patients in group B, 4 (17%) had an increase in positive skin test results, 7 (30%) decreased, and 12 (52%) showed no change.

GM-CSF Side Effects

Patients who received GM-CSF were monitored for adverse events during the course of each 7-day injection cycle. As summarized in Table IV, adverse events reported were typical of biological therapies and included local reactions, fatigue, bone pain, myalgia, and fever. Most cases of adverse events were of mild severity, although formal NCI toxicity scale grading was not evaluated. For the entire study population, local reaction occurred in 39% of subjects, fatigue in 30% of subjects, pain in 24% of subjects, and fever in 7% of subjects. Of the 44 patients who received GM-CSF, 23 patients completed six full 7-day cycles of GM-CSF and vaccine, 11 patients discontinued GM-CSF due to adverse events, and 10 subjects were withdrawn from the study for disease progression (Table V).

DISCUSSION

Our results suggest GM-CSF as employed in this study did not detectably enhance clinical response to DC-peptide infusions. There was no increased incidence of complete or partial responders in patients who received GM-CSF in groups A-I, A-II, or B (Table I). In groups A-II and B, repeat skin tests did not detect a significant enhancement of immune responses due to GM-CSF (Table III). The absence of benefit in this study contrasts with other reports that suggested significant improvements in antigen-specific immune response following vaccination with GM-CSF. These reports differed from our study in GM-CSF dose, duration of dosing, and dosing relative to vaccination. These may be variables that need to be evaluated with dendritic cell-based vaccines as well.

Groups A-I and A-II (patients with hormone-refractory metastatic prostate cancer) had more advanced disease at the start of the clinical trial, compared to group B (patients with locally recurring prostate cancer) (Table II). The mean PSA values for groups A-I and A-II were higher than the mean PSA values for group B. The mean hematocrit values for groups A-I and A-II were below normal range, while the mean hematocrit values for group B were normal. The mean PSMA values for groups A-I and A-II were also higher than for group B. The mean age for group A-I was higher than in groups A-II and B.

There were no statistically significant differences in mean values of PSA, PSMA, hematocrit, lymphocyte count, or age between patients who received GM-CSF and those who did not, within groups A-I, A-II, or B (Table II). The mean PSA for group A-I with GM-CSF was higher than for group A-I patients who did not receive GM-CSF. The same was true for group B. However, for group A-II the mean PSA for patients with GM-CSF was lower than for group A-II patients who did not receive GM-CSF. These comparisons demonstrate that there was no significant difference in terms of these factors between patients who received

TABLE IV. GM-CSF Side Effects Summary Report*

Group		Reported occurrences of side effects							
		Local reactions		Fatigue		Pain		Fever	
A-I	(17 patients)	19	26%	27	36%	25	34%	3	4%
A-II	(13 patients)	29	38%	25	33%	17	22%	5	7%
B	(14 patients)	46	50%	20	22%	16	17%	10	11%
Total	(44 patients)	94	39%	72	30%	58	24%	18	7%

*Percentages are based on total number of side effect occurrences reported for each group, or for the total study population, respectively.

TABLE V. GM-CSF Summary Report*

Group	Total patients	GM-CSF no	GM-CSF yes	Completed GM-CSF	Discontinued GM-CSF	Discontinued due to	
						Side effects	Off study
A-I	33	16	17	9	8	4	4
A-II	25	12	13	6	7	1	6
B	37	23	14	8	6	6	0
Total	95	51	44	23	21	11	10

*GM-CSF no, patient received no injections of GM-CSF; GM-CSF yes, patient received at least one injection of GM-CSF. GM-CSF discontinuation due to: side effects, GM-CSF side effects led to patients' discontinuation of GM-CSF; off study, patients discontinued study participation due to disease progression.

GM-CSF and those who did not, within each of the groups (A-I, A-II, and B).

Most reported side effects were of mild severity. There were no cases of severe side effects, and few cases of moderate side effects. In this open-label study of selected subjects, the incidence of adverse events was biased by both direct patient reporting and absence of blinded observers. Patients in group A-I reported more instances of fatigue and pain than of local reaction. This may be partly due to the more advanced stage of disease in group A-I as a whole. Group A-I patients had a lowered immune response as judged by DTH skin test, which may explain why they had less local reaction to injection than patients in groups A-II or B. Group A-I patients' more advanced disease may also have caused them to be more susceptible to bone and muscle pain, and fatigue. Side effects were reported only by patients who received GM-CSF. In the case of group A-I patients, all patients previously participated in a phase I clinical trial in which they received infusions of DC and PSMA peptides. Mild to moderate transient hypotension on the day of infusion was the only side effect reported during the phase I study [12]. Patients from the phase I study who also participated in this phase II study (group A-I) experienced side effects when systemic GM-CSF treatment was added to the DC-peptide infusion treatment. Although there is no definite correlation between the reported side effects and GM-CSF, these circumstances suggest that the side effects were most likely due to GM-CSF treatment. Our results should be interpreted with caution in light of published reports in many clinical settings demonstrating the safety of GM-CSF administration. These events may have resulted from the combination of GM-CSF with our dendritic cell vaccine or from chance, since none were statistically significant.

Cases of side effects causing discontinuation were subject to patients' levels of discomfort and were not severe by definition. A side effect leading to discontinuation does not necessarily categorize it as more severe, as patient interpretations and willingness to endure discomfort vary, and patients' continuation of GM-CSF as an adjuvant treatment was voluntary. It is possible that discomfort caused by the use of GM-CSF in elderly prostate cancer patients is not as well-tolerated as in younger prostate cancer patients, or younger cancer patients in general. Age and quality of life may be very significant factors in a patient's willingness to tolerate mild or moderate side effects.

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